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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,617	02/21/2002	Steffen Panzner	101215-81	9573

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 02/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,617	PANZNER ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-13 and 21-59* is/are pending in the application.

4a) Of the above claim(s) *12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11 and 21-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-25-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 11-25-05 is acknowledged.

The claims included in the prosecution are 1-3, 5-11 and 21-59.

1. In view of amendment to the claims introducing 'neutral lipid', the 102 rejection has been withdrawn.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 3, 5-12 and 21-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant amends claim 1 to recite the presence of one amphipathic lipid with a positive charge, one amphipathic lipid with a negatively charge. Claim 3 recites the presence of an amphipathic lipid **with both a positive charge and a negative charge.** Also claim 3 recites the isoelectric point of between 4 and 8 whereas the range recited in claim 1 is 4-7. Claim 3 is not further limiting with respect to the amphipathic lipid and the isoelectric point.

As pointed out above, applicant amends claim 1 to recite the presence of one amphipathic lipid with a positive charge, one amphipathic lipid with a negatively charge. Claim 5 recites 'further comprise at least one amphipathic molecule with a positive charge or at least one amphipathic molecule with a negative charge'. The distinction

between the amphipathic lipid and the amphipathic molecule recited in claim 5 is unclear.

'the anionic lipid' and the cationic lipid' in claims 23, 33, 39 lack an antecedent basis in claim 1.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-3, 5-11 and 21-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hafez cited above in combination with Huang (5,283,122) or Lishko (5,753,263).

Hafez discloses large unilamellar liposomes containing cholesteryl hemisuccinate (CHEMS) and DODAC. The pH values are from 4 to 6.7. The sizes of the liposomes are either 153 + 34 nm or 274 nm depending upon the ratios of DODAC and CHEMS (abstract, Materials and Methods and Results). What is lacking in Hafez is the inclusion of a neutral lipid such as cholesterol or phosphatidylcholine.

Huang while disclosing pH sensitive liposomes teaches that inclusion of cholesterol decreases the leakage and the less leaky liposomes containing cholesterol will be particularly useful in discharging their contents into the cytoplasm. The contents

include drugs, enzymes, hormones and others. The anionic lipid is phosphatidic acid or oleic or palmitic acid (abstract, col. 5, lines 16-68, col. 6, lines 25-54).

The inclusion of a neutral lipid such as cholesterol in the liposomes of Hafez would have been obvious to one of ordinary skill in the art since such liposomes are less leaky and discharge the contents in the cytoplasm after fusion as taught by Huang. What is also lacking in Hafez is the inclusion of the active agents in the liposomes. However, in the Discussion section (page 1449, col. 1), Hafez suggests the applicability of the liposomes for the delivery of nucleic acids and therefore, it would have been obvious to one of ordinary skill in the art to encapsulate an active agent in the liposomes of Hafez with a reasonable expectation of success. Hafez is also lacking in the teachings of instant sizes between 60 and 130 nm. However, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to prepare liposomes of desired sizes depending upon the goal by manipulating the sonicating conditions. Furthermore, Hafez also teaches that the liposomal sizes can be varied by varying the ratios of the lipids and the liposomal sizes of 153 with a standard deviation of 34 (153-34 = 119) fall within the sizes claimed in instant claim 22. Although Hafez does not teach instant cationic lipids such as HisChol, it would have been obvious to use art known compounds in the liposomes of Hafez with the expectation of obtaining similar results since the principle is the same.

6. Claims 1-3, 5-11 and 21-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hafez cited above in combination with Lishko (5,753,263).

Hafez discloses large unilamellar liposomes containing cholesteryl hemisuccinate

(CHEMS) and DODAC. The pH values are from 4 to 6.7. The sizes of the liposomes are either 153 + 34 nm or 274 nm depending upon the ratios of DODAC and CHEMS (abstract, Materials and Methods and Results). What is lacking in Hafez is the inclusion of a neutral lipid such as cholesterol or phosphatidylcholine.

Lishko while disclosing pH sensitive liposomes teaches that the pH sensitive liposomes can be formed by combining phosphatidylcholine or cholesterol with one or more phospholipids to form pH sensitive liposomes Lishko further teaches that pH sensitive liposomes contain DOPE and Cholesterol hemisuccinate (col. 15, lines 13-38).

To include either phosphatidylcholine or cholesterol in the liposomal compositions of Hafez with a reasonable expectation of success, would have been obvious to one of ordinary skill in the art since Lishko advocates the use of these in pH sensitive liposomes. Although Hafez does not teach instant cationic lipids such as HisChol, as pointed out above, it would have been obvious to use art known compounds in the liposomes of Hafez with the expectation of obtaining similar results since the principle is the same.

7. Claims 1-3, 5-11 and 21-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deshmukh et al (6,258,792).

Deshmukh while disclosing cationic cholesteryl derivatives teaches that while formulating liposomes these cationic cholesterol derivatives may be combined with DOTAP, anionic lipids such as phosphatidic acid and neutral lipids such as DOPE and cholesterol. The biologically active agents include DNA, RNA or proteins. The liposome sizes are between 100 and 200 nm. (Abstract, col. 4, line 45 through col. 6, line 43

through col. 7, line 41; col. 7 line 46 through col. 8, line 50, col. 10, Examples). According to Deshmukh, the negatively charged lipid can be included so long as the net charge of the complexes formed is positive. It would have been obvious to one of ordinary skill in the art to prepare liposomes containing cationic lipid, anionic lipid and a neutral lipid based on the suggestion of Deshmukh et al with a reasonable expectation of success. The liposomes of Deshmukh et al would show the same isoelectric point since Deshmukh is suggestive of the same components and provide guidance for the preparation of liposomes with a reasonable expectation of success. Although Deshmukh does not teach liposomes having a overall negative charge at the physiological pH, since he teaches that a negatively charged lipid is included in the liposomes containing a cationic lipid as long as the resultant liposome is cationic, one of ordinary skill in the art would be motivated to vary the amounts of the cationic lipid and the anionic lipid as in instant claims to obtain a liposome with desired net positive or negative charge at physiological pH, depending upon the use of the liposome. Although Deshmukh does not teach instant cationic and anionic lipids such as HisChol and CHEMS respectively, it would have been obvious to use art known compounds in the liposomes of Deshmukh with the expectation of obtaining similar results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that what is taught by Deshmukh is cholesterol hemisuccinate choline ester (ChOSC) wherein the choline moiety is connected to the 3-hydroxyl group via a succinyl spacer arm and does not teach CHEMS. These arguments are not found to be persuasive since, as pointed out above, Deshmukh is

suggestive of the combination of a cationic and anionic amphipathic lipids together with a neutral lipid just as in instant claim 1.

8. Claims 5-11, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hafez cited above, in view of Deshmukh cited above.

The teachings of Hafez have been discussed above. What are lacking in Hafez are the teachings of the inclusion of a neutral lipid and the inclusion of an active agent. Deshmukh as pointed out above, teaches that a neutral lipid can be included in the liposomes containing a cationic lipid and anionic lipid. Deshmukh also teaches the use of these liposomes for the delivery of active agents such as DNA, RNA and proteins. It would have been obvious to one of ordinary skill in the art to include a neutral lipid or encapsulate active agents such as nucleic acids or proteins in the liposomes of Hafez with a reasonable expectation of success since Deshmukh teaches that neutral lipids can be included in the liposomes and these liposomes can be used to encapsulate nucleic acids and proteins.

Applicant's arguments are not found to be persuasive. Applicant argues that the teachings of Hafez and Deshmukh cannot be properly combined because these references have different requirements that are mutually exclusive. According to applicant, Hafez teaches the creation of anionic liposomes at physiological pH and Deshmukh requires cationic liposomes. These arguments are not persuasive since the neutral lipid suggested by Deshmukh does not contribute any charge at all at the physiological pH.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/ S Kishore

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GSK